Guidance for Industry

Monoclonal Antibodies Used as Reagents in Drug Manufacturing

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
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U.S. Department of Health and Human Services
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Draft - Not for Implementation

GUIDANCE FOR INDUSTRY[1]

Monoclonal Antibodies Used as Reagents in Drug Manufacturing

(Due to the complexity of this draft guidance, please identify specific comment by line number. Please use the pdf version whenever possible.)

I. INTRODUCTION

This guidance is intended to provide recommendations to sponsors and applicants on the use of monoclonal antibodies (mAbs) as reagents in the manufacture of drug substances and drug products which are regulated by the Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER). The guidance focuses on the chemistry, manufacturing, and control (CMC) issues that should be addressed in investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug marketing applications (ANDAs), biologics license applications (BLAs), and supplements to these applications.

This document is not intended to cover mAbs that are used as diagnostic, radiolabeled imaging agents, or therapeutic products. For a discussion of mAb products for human therapeutic use please refer to the *Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use* (PTC 1997), available from CBER. The recommendations for characterization and testing for mAbs used as parenteral pharmaceuticals are by necessity very stringent, and not all of them would be applicable to mAbs that are used as reagents in drug manufacturing.

II. BACKGROUND

A. DEFINITION

Monoclonal antibodies are immunoglobulin molecules (IgG, IgM, IgA, IgE) that are

[1] This guidance has been prepared by the Monoclonal Antibodies Working Group of the rDNA Reagent Technical Committee of the Complex Drug Substances, Excipients, and Reagents Coordinating Committee (CDS CC) in the Center for Drug Evaluation and Research (CDER), with input from the Center for Biologics Evaluation and Research (CBER), at the Food and Drug Administration. This guidance document represents the Agency's current thinking on monoclonal antibodies used as reagents. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative may be used if such approach satisfies the requirements of the applicable statute, regulations, or both.

secreted from a population of identical cells (i.e., cloned cells). The commercial utility of these highly specific molecules lies in the simplicity by which large quantities of IgG or other antibodies with identical binding sites are generated by in vivo or in vitro methods. The technique of Köhler and Milstein (1975 and 1976) involves immortalizing antibody-producing plasma cells from an immunized mouse by fusion with myeloma cells (a plasma cell tumor line). The resulting hybrid cells or hybridomas can be maintained in vitro or in vivo to continuously secrete large quantities of mAb with a defined specificity, which can be purified and used in a variety of applications.

This guidance presents issues and concerns associated with mAbs generated by the hybridoma technology, and production of recombinant mAb or their fragments in bacteria, yeast, and nonprimate animal-derived cell lines. Monoclonal antibodies or their fragments generated by other methods may present additional concerns specific to the particular process used.

B. PURPOSE AND SCOPE

The scope and issues related to mAbs used as reagents are somewhat different from those of mAbs used as parenteral therapeutic agents. For an mAb reagent, the primary emphasis is on assessment of the following issues:

- Performance characteristics of the mAb reagent during drug substance manufacture

- Biological safety, in particular the assessment of contamination of the mAb with adventitious agents from the source of origin and those introduced during mAb production. This evaluation may take into account the overall manufacturing process from mAb reagent through the final drug substance and/or product.

- Potential presence of residual amounts of the mAb reagent in the final drug substance and/or product

The recommendations in this guidance focus on the use of mAbs in the drug substance or drug product manufacturing process where the mAb reagent is used to purify the drug substance and/or drug product. The extent of characterization required for the mAb reagent depends on the nature of the steps that follow use of the mAb and thus will vary among applications. While many CMC concerns regarding certain mAb reagents may be unique to biotechnology-produced reagents, the general concepts expressed in the *FDA Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances* (FDA 1987) are also applicable and should be used as guidance. Because the extent of testing and characterization of the mAb reagent is

determined on a case-by-case basis, an early and continued dialogue between the applicant and the Agency is encouraged as a method of addressing these issues.

III. PRODUCTION OF MONOCLONAL ANTIBODIES

The applicant should provide an adequate description of the manufacturing technology used for production of the mAb reagent. This is important to ensure satisfactory performance of the reagent during production of the drug substance and also to assess its potential impact on the biological safety, quality, and purity of the drug product.

A. PRODUCTION ISSUES

The predominant concern with the use of an mAb in drug substance and drug product manufacture is the introduction of contaminants and adventitious agents (e.g., bacteria, fungi, viruses, mycoplasma, protein contaminants) that are not removed by the manufacturing steps subsequent to the introduction of the mAb reagent in the process stream. These subsequent steps may vary widely depending on the manufacturing processes for the drug substance and drug product. They may range from those which involve direct final drug formulation and filling without much processing to those that may include extensive processing steps (e.g., extraction and/or chromatography with organic solvents, heat inactivation) that are likely to remove and/or inactivate potential microbial contaminants introduced by the mAb reagent. Thus, the appropriate microbial testing of the mAb reagent and the mAb secreting hybridoma cells will depend on the manufacturing process of the drug substance and the step in which the mAb reagent is used. In addition, the type of the manufacturing facility (e.g., biological versus pharmaceutical) where the mAb reagents are used should be considered and evaluated for the possibility of cross-contamination with adventitious agents which may be in the cell lines and reagents. Consequently, appropriate biological safety characterization for individual mAb reagents should be determined on a case-by-case basis. Because most biotechnology-derived and biological products are heat labile by nature and easily degradable by a range of chemical treatments, processing steps such as autoclaving or chromatography with organic solvents are unlikely to be successfully incorporated into the manufacturing process of a biologic. Therefore, CDER and CBER anticipate that most reagents used in producing biotechnology products or biologics will be processed to minimize microbial contaminants and will be rigorously tested for adventitious agents (see PTC 1997, sections II.B and C).

Adequate characterization and assessment of the identity, purity, and structural integrity of the mAb reagents are vital to their efficient and uninterrupted performance during production of drug substances and drug products. Affinity and specificity studies are recommended to assess whether the characteristics of an mAb reagent are optimal for

targeted binding to their appropriate substrate during the manufacture of the drug substance.

Typical production of monoclonal antibodies includes the following four phases:

- Development and characterization of the cell line
- Establishment of the cell banks
- Production in the cell/tissue culture or in animals (ascites fluid)
- Isolation and purification.

A summary of the critical points specific to mAbs used as reagents in drug manufacturing is provided below.

1. Development and Characterization of the Cell Line

Development of the cell line should be adequately described in the application. This information is important because it will determine, in part, what adventitious agent testing should be performed in those cases where extensive testing may be necessary. Characterization of the chemical and physical properties of the monoclonal antibody should take place at this stage. Avidity and specificity for the target molecule should be demonstrated to ensure that the mAb reagent will bind specifically to its appropriate substrate during manufacturing of the drug substance. In those cases where an exact numerical evaluation of avidity cannot be determined, some assessment of binding strength should be made. The degree of acceptable analysis for mAb specificity will vary depending on the application. Greater characterization may be needed for applications where the mAb reagent is used to purify a drug substance from a mixture containing structurally similar molecules. Other characterization of the mAb reagent, such as subclass and molecular weight determination, should be performed early so that appropriate identity tests can be developed for production lots.

2. Establishment of the Cell Banks

Major concerns in cell bank establishment include verification of the identity and clonality of the banked cells and acceptable degree of freedom from adventitious agents. The extent of recommended characterization of the cell banks depends on the type of facilities in which the cell banks and/or reagents are used and the manufacturing processes employed.

Facilities that produce biologicals, culture cells, or process biological source material could become contaminated with adventitious agents introduced into the

facility by mAb cell banks which could then propagate. Thus, cell banks that are brought into biologics or biotechnology facilities should be fully characterized for adventitious agents. Cell banks used to produce reagents that are later transferred to a biologics facility should also be fully characterized for adventitious agents (see PTC 1997, sections II.B.1 and II.C.1).

For drug substance manufacturing processes that include a terminal sterilization step (e.g., autoclaving) or downstream processing with organic solvents (e.g., extraction, chromatography), the degree of cell bank characterization needed may include only those tests that assure successful continuous culture during production (e.g., sterility, mycoplasma, and in vitro co-cultivation for adventitious agents). In these instances, the downstream steps in the manufacturing process should be validated, using a challenge test, for their capacity to sterilize potential adventitious agents or contaminants that are introduced by the reagent. Exposure to some organic solvents may be validated for viral removal and/or inactivation, while exposure to other solvents may not accomplish this goal. For the purpose of this document, *sterilization* means complete inactivation or removal of all potential adventitious agents.

For drug substance manufacturing processes where the use of the reagent is not followed by a downstream, validated sterilization step, a complete characterization of the cell banks should be performed (see PTC 1997, sections II.B.1 and II.C.1).

3. Production in the Cell/Tissue Culture or in Animals (Ascites Fluid)

Monoclonal antibodies for use as reagents are typically produced by growth of the hybridoma cell line in cell culture or in animals (ascites fluid). In general, steps should be taken to prevent or control contamination (e.g., virus, bacteria, fungi, mycoplasma, transmissible spongiform encephalopathy (TSE)) introduced during the production process. Recommended characterization of the mAb production process again will depend on the subsequent downstream processing of the drug substance.

For drug substance manufacturing processes ***with*** a downstream sterilization step that can be validated, the major concern with adventitious agents is that they do not contaminate the mAb production culture and possibly interrupt the flow of production of the mAb reagent. However, special consideration should be given to a potential contamination of the drug product with difficult to detect hazardous agents that may be introduced from animal-derived sources, because some of these agents have been shown to survive extreme conditions (e.g., TSE). All bovine media components should originate from source herds from countries free of

bovine spongiform encephalopathy (BSE). Also, the use of human-derived media components is discouraged because of the potential of contamination with pathogenic agents (e.g., Creutzfeldt-Jacob disease (CJD)).

In contrast, for drug substance manufacturing processes ***without*** validated downstream sterilization, more extensive safety precautions are recommended (see PTC 1997, sections II.B.2 and 3 and II.C.2).

Consistent production of the mAb during fermentation should be monitored to assure uninterrupted downstream production of the reagent and relevant drug substance. Changes in the rate of secretion of mAb by the hybridoma substrate should be investigated.

4. Isolation and Purification

The isolation and purification processes of mAbs vary, with some mAbs being subjected to several purification steps, while others only a few. Usually, purification involves one or more chromatography steps, often accompanied by filtration or precipitation steps. Again, concerns and recommendations vary with the drug manufacturing process.

For drug substance manufacturing processes with a downstream sterilization step that can be validated, the major concern with adventitious agents in reagent purification is the bioburden. The bioburden should be kept sufficiently low to ensure successful purification of active mAb reagent.

For drug substance manufacturing processes without a validated sterilization step, more extensive safety precautions are recommended (see PTC 1997, sections II.B.4 and II.C.4-6). This includes the validation of the inactivation and/or removal of retroviruses.

When purification processes for mAb reagents are relaxed in comparison to those used for parenteral products, a product with more protein and/or nucleic acid contaminants may result. For reagents, the predominant concern is whether the mAb purity is sufficient to prevent the carryover of in-process contaminants to the drug substance and/or product. Consistent production of reasonably pure reagent should be demonstrated to assure adequate and uninterrupted performance in the production of the drug substance. Downward trends of the mAb lots in purity, integrity, and binding properties should be thoroughly investigated. Chemical impurities originating from buffers, columns, and media, as well as host cell

proteins, should be monitored and minimized to avoid contamination of the bulk drug substance.

B. REFERENCE STANDARD

1. Definition

The reference standard consists of an adequately purified preparation of a free monoclonal antibody on which extensive structural characterization and testing have been performed.

2. Responsibility

A reference standard should be maintained in the monoclonal antibody manufacturing facility. Characterization and shelf-life testing of the mAb reference standard should be performed by the mAb manufacturer and/or supplier.

3. Characterization

Characterization of the reference standard should be performed on free monoclonal antibody, (i.e., not linked to a solid support). The results should be used as reference data for the identity, purity, and binding properties of the mAb to ensure that routinely manufactured lots of mAb have sufficient avidity and specificity and perform adequately during the manufacture of the drug substance. The following tests are typically used:

a. Tests for Identity

Molecular Weight

Molecular weight of the whole mAb molecule as well as its subunits (i.e., light and heavy chains) and possible oligomers should be determined by using a combination of appropriate methods (e.g., sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) in reducing and nonreducing conditions, size exclusion high performance liquid chromatography (HPLC)).

Immunoglobulin Class and Subclass Identification

The class and subclass identification may be determined for the mAb reagent itself or for the monoclonal antibody-producing cell line.

Generally, this can be accomplished on the reagent by using a combination of SDS-PAGE and Western blot analysis with anti-isotype antibodies or by isotype-specific enzyme-linked immunosorbent assay (ELISA). The fluorescence-activated cell-sorting (FACS) analysis is often used when the identification is performed on the hybridoma cell line.

Isoelectric Focusing (IEF) Profile

IEF is a sensitive method for detecting changes in protein structure relative to their ionic charge, such as alteration of carbohydrate content, de-amidation and a wide range of other modifications.

b. Tests for Affinity and Specificity

A measurement of the avidity or binding strength of the antibody for its antigen should be performed. Relevant techniques include radioimmunoassay (RIA), competitive binding using ELISA, measurements of binding-induced fluorescence changes in protein or ligand, and surface plasmon resonance. The affinity measurement can assist in determining whether the antibody has sufficient binding strength to perform adequately in manufacturing. The degree of cross-reactivity of the monoclonal antibody should be quantified by measuring the competition with closely related target molecules that may be present in the drug substance.

c. Tests for Purity

The purity of the reference standard should be determined by an adequate method or combination of methods (e.g. chromatography, electrophoresis, capillary electrophoresis). The reference standard should be assessed for aggregates, chemical impurities, degradation products, and foreign proteins, such as host cell proteins or proteins derived from the culture media. SDS-PAGE gel with Coomasie Blue, Silver or Gold staining is considered sufficient for routine monitoring of contaminating proteins. For most uses the absolute purity of the reagent is not a critical requirement; however, more sensitive or specific immunoassay methods and/or analytical HPLC should be used in appropriate circumstances.

d. Acceptance Criteria and Tests

The specifications sheet listing all tests and acceptance limits for the reference standard should be provided. A certificate of analysis (COA) or

compilation of analytical results should be submitted in the application. The COA should contain data for the complete set of tests, including the protein concentration and the ratio of monoclonal antibody to protein.

C. PROCESS VALIDATION

The degree of process validation for the reagent manufacturing process will vary with the reagent use. At a minimum, it should be demonstrated that the manufacturing process can consistently produce reasonably pure and active mAb reagent. For reagents used in drug manufacturing processes that lack validated downstream sterilization steps, microbial process validation procedures recommended in the PTC 1997 document are appropriate for the reagent, including validation of the removal of retroviruses. The validation of virus removal may be performed during one of the steps in the reagent manufacture, during one of the steps in the drug substance manufacture downstream of the addition of mAb reagent, or during one of the steps related to the reagent preparation, such as linking the reagent to a column or column sanitization.

Depending on the intended use, the manufacturer of the reagent may wish to file a drug master file (DMF) for the mAb reagent. A COA should be available for each individual reagent lot. A copy of a representative COA should be included in the application. Each certificate of analysis should contain the following disclaimer statement in large bold lettering: **Reagent use only; not intended for parenteral use or for ex vivo manipulation of human cells that are re-introduced into humans.** If the reagent has not undergone validated virus removal steps, the supplier should indicate this on the COA. In cases where a downstream validated sterilization step is absent in the drug substance manufacturing process, reagents produced in a manufacturing process that has not been validated should be tested for adventitious agents produced by the mAb cell culture (e.g., endogenous retroviruses) prior to introduction into the drug substance facility.

IV. ACCEPTANCE CRITERIA AND TEST METHODS FOR MONOCLONAL ANTIBODIES

A. ACCEPTANCE CRITERIA AND TEST METHODS FOR FREE MONOCLONAL ANTIBODIES

Based on manufacturing experience and intended use of the mAb reagent, the supplier should establish a set of tests and acceptance criteria to adequately evaluate the free mAb (see section III.B.3, Characterization). The test results for an individual lot of the reagent should be compared to the reference standard (see III.B above). Testing should typically include:

- Appearance
- Identification (for example, SDS-PAGE pattern and IEF profile)
- Purity (for example, HPLC, SDS-PAGE with Coomasie Blue, Silver or Gold staining, capillary electrophoresis, or other appropriate techniques). Although purity is not as critical for reagents as for pharmaceutical products, an assessment of the percentage purity of each lot of mAb reagent should be made. Appropriate characterization and acceptance criteria for chemical impurities as well as host cell proteins should be included, unless acceptable validation data for their removal during the manufacturing process of mAb or drug substance are submitted.
- Protein concentration
- Binding strength avidity to the target molecule
- Microbial limits or bioburden
- Bacterial endotoxins
- Preservatives. Vendors of mAb reagents often supply the reagents in a buffer solution with a preservative (e.g., sodium azide). Testing for levels of preservatives should be considered, but would depend on the type of preservative agent and amount of validation data submitted for the preservative removal either before or during the drug substance manufacture.

B. ACCEPTANCE CRITERIA AND TEST METHODS FOR MONOCLONAL ANTIBODIES LINKED TO SOLID SUPPORT

At a minimum, tests and acceptance criteria for the monoclonal antibody linked to a solid support should include the following:

- Appearance
- Surface density of mAb (e.g., milligrams of mAb per gram of resin)
- Specific binding capacity at a specified pH range and temperature for optimum antibody performance
- Integrity of solid support. The type of the solid support and recommended experimental conditions for optimum performance of mAb linked to particular

solid support (e.g., pH, temperature, solvent, re-use) should be provided. Limits on the rates of leaching of mAb, preservatives (e.g., sodium azide), and solid support components at permitted experimental conditions should be specified.

- Column performance. Maximum load, number of times the column can be used, method of regeneration, and bioburden and/or bacterial endotoxin specifications after each use should be defined.

C. CERTIFICATE OF ANALYSIS

The supplier of the monoclonal antibody should provide a COA to the drug substance manufacturer. In the case of monoclonal antibody linked to a solid support, a COA should be provided for both, free and linked forms. This should include data collected according to the complete set of tests and comparison to the reference standard. The total protein concentration and a ratio of monoclonal antibody to protein (i.e., milligrams of mAb to milligrams of protein) should be included. Also, a list of tests for adventitious agents and test results performed on the mAb reagent and/or its cell banks should be included in the COA.

D. ACCEPTANCE CRITERIA FOR COMMERCIAL mAb REAGENT

The drug substance manufacturer should establish appropriate tests and acceptance criteria for the mAb reagent, and perform testing before employing it in the manufacturing process. At a minimum, a validated identity test and a test for binding activity should be performed. Microbial testing that includes tests for adventitious viruses should be performed, if appropriate. In many cases, the drug substance manufacturer may not be supplied with the reference material by the distributor of the reagent. Consequently, reduced acceptance testing may have to be done in the absence of an authentic standard. In some cases, a substitute reference standard can be qualified by the drug substance and/or product manufacturer. The appropriateness of the reference standard used for the acceptance testing will be determined on a case-by-case basis.

V. MONOCLONAL ANTIBODIES IN DRUG MANUFACTURING

A major use of mAb reagents is in the purification of drug substance by an mAb that is attached to a solid support (e.g., immunoaffinity chromatography). A typical example is discussed below. Other possible applications for the use of mAb reagents in drug manufacture will be evaluated on case-by-case basis.

A. PURIFICATION OF DRUG SUBSTANCE

The purification process should be briefly described and should include the source and chemical characterization of the solid support, the method of attachment of the mAb to the solid support, and the affinity of the mAb for the drug substance. If applicable, a letter of authorization (LOA) from the DMF holder should be provided for cross-referencing the supportive proprietary data. For immunoaffinity columns, the surface density of the antibody (e.g., milligrams of mAb per gram of resin) should be provided, and testing for leachables, including the mAb, from the column into the eluant, should be performed. Finally, general information regarding the chromatographic system, such as column preparation method, column binding capacity, column lifetime, column storage and regeneration conditions, the maximum number of column usage cycles, working conditions, buffers used during operation, and the yield of the purified drug substance should be provided. Validation for the ability of the affinity column to achieve the intended purification under described working conditions should be carried out.

B. TESTS AND ACCEPTANCE CRITERIA

Tests and acceptance criteria for residual monoclonal antibody should be included in the specification sheet of the drug substance that was processed with the mAb reagent. Residual mAb may be present in the drug substance and, consequently, in the drug product as a result of the leaching of mAb from a solid support, or carry-through from a process stream to which free monoclonal antibody has been added. Residual mAb should be monitored by a sensitive and specific assay (e.g., ELISA). Tests and acceptance criteria for other process-related impurities (e.g., growth media components, preservatives, solid support material, bioburden, endotoxins) may also be necessary in some circumstances.

C. COMPARABILITY

Changes in the mAb supplier or changes in the manufacturing process of mAb or solid support are considered to be drug substance manufacturing process changes which may have an effect on the biological safety and effectiveness of the drug substance and, consequently, the final product. Appropriate product comparability testing should be performed in cases where significant changes have been implemented in the mAb manufacturing process that may change the purity or the performance of the reagent (e.g., changes in specificity, avidity, or microbiological safety). The guidance document entitled *FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products* contains a discussion of comparability testing for mAbs used parenterally. Testing recommended for parenteral therapeutics is necessarily stringent. In contrast, comparability testing for mAb reagents should focus mainly on the performance characteristics of the reagent and its purity and stability. This is particularly important when changes in the reagent manufacture will

likely have an impact on the biological safety, purity, quality, and stability of the drug substance and/or drug product.

VI. STABILITY OF MONOCLONAL ANTIBODIES

A. STABILITY DURING STORAGE

The supplier should perform adequate stability studies on the monoclonal antibody. The mAb binding capacity and integrity of the protein structure should be monitored using the same criteria as for the mAb lot release. In the case of monoclonal antibody linked to a solid support, stability studies should be performed on both free and linked forms. Based on these studies, the mAb supplier should determine and provide an expiry date for each lot of monoclonal antibody. The International Conference on Harmonisation (ICH) documents entitled *Stability Testing of New Drug Substances and Products* (ICH Q1A) and *Quality of Biotechnological Products: Stability Testing of Biotechnological/Biological Products* (ICH Q5C) outline basic recommendations for stability protocols and testing which are generally applicable to mAb reagents. Stability testing of mAb reagent should focus mainly on performance factors such as binding capacity, protein integrity, and testing for microbial contaminants.

B. STABILITY DURING USE

The stability of an mAb reagent during its use in production of a drug substance and/or product should be determined by the drug substance or product manufacturer and should be specified in the master batch record. Specific tests and parameters depend on the manner in which the antibody is linked to the solid support and the antibody's load per weight of solid support. The method for monitoring the column performance should be adequately described in the application. Column performance should be validated with regard to, for example, the storage conditions, the number of times a column is used, and the regeneration process. (For more information, please refer to sections IV.B and V.A of this document).

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